KALEIDOSCOPIC NERVOUS SYSTEM INVOLVEMENT IN THE SETTING OF A CHRONIC MULTISYSTEM DYSIMMUNE DISORDER: REPORT OF A REMARKABLE CASE

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ABSTRACT

Background. Neurological manifestations are not an unusual expression of multisystem dysimmune disorders, some etiopathogenic correlations being more common than others. We report here four distinct patterns of recurrent central nervous system (CNS) involvement and neuromuscular junction dysfunction occurring in an autoimmune chronic disease. Our patient presented diagnosis clues suggestive for systemic lupus erythematosus, antiphospholipid syndrome and Sjögren's syndrome along with clinical findings highly characteristic for two primary vasculitides (i.e. Churg-Strauss syndrome and Behçet's disease) and an increased susceptibility to infections. To our knowledge no similar case has been described previously.

Case presentation. The patient is a Caucasian female of current age 26. Her neurological condition evolved over the last 6 years in a relapsing-remitting manner with recurrent cerebral venous system thrombosis/thrombophlebitis, recurrent myelopathy consistent with acute transverse myelitis, recurrent encephalopathy manifested as psychosis, recurrent pancerebellar syndrome and recent onset myasthenic syndrome. In spite of reaching life-threatening illness severity several times, following each one of the disease flare-ups the patient eventually showed a complete clinical resolution with therapy, as a peculiar and unexpected feature of her repeated CNS autoimmune attacks.

Conclusion. When facing a complex and atypical immune disorder involving CNS one should remain cautious in labeling it. In such beyond-guidelines cases several treatment approaches should be tried and reevaluation of different organ involvement is a must.

Key words: antiphospholipid, autoimmune, Behçet's, cerebellar syndrome, thrombosis, myasthenic, myelitis, Sjögren's, lupus

BACKGROUND

Neurological involvement at one or more levels, ranging from innocuous to severe and having various etiopathogenic pathways that result in unifocal, multifocal or diffuse injury (either as a direct consequence or secondary to other organ impairment and/or to drug administration) are not unusual in most multisystem dysimmune disorders. Systemic lupus erythematosus is commonly associated with a wide spectrum of nervous system dysfunction, from stroke with several potential underlying mechanisms to myelitis, and peripheral neuropathy (1,2). As expected, the presence of antiphospholipid antibodies may result in ischemic central nervous system events (i.e. stroke and sometimes transverse myelopathy), nevertheless also appearing to be related to other neurological manifestation such as chorea (1,3). Sjögren's syndrome is associated both with central and peripheral nervous system involve-

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ment, polyneuropathy, myelopathy/myelitis, autonomic impairment and cognitive dysfunction being among the most commonly reported (1,4). The neurological involvement in Behçet's disease encompasses parenchymal and vascular central nervous system involvement, the former having a predilection for the brainstem and basal ganglia and the latter for the dural sinuses (5,6). Churg-Strauss syndrome commonly results in peripheral nervous system involvement, the concurrence of central nervous system impairment being very seldom reported (1,7). The acquired autoimmune myasthenic syndromes may be associated either with other autoimmune diseases or with a neoplastic trigger (8,9).

We report here the case of a 26 years old Caucasian female with recent onset myasthenic syndrome and at least four distinct patterns of reversible central nervous system involvement (i.e. cerebral venous system thrombosis/thrombophlebitis, myelopathy consistent with acute transverse myelitis, encephalopathy manifested as psychosis, and pancerebellar syndrome accompanied by mild cerebellar atrophy) recurring several times in the setting of an ongoing multisystem dysimmune disorder.

CASE PRESENTATION

Overview

The patient is a Caucasian female, of current age 26. She is HLA B51 and HLA B27 negative. No data are available concerning the medical history of her relatives except for her mother which had atopic conditions. The medical records regarding her early childhood note febrile seizures up to the age of 5 without offering any further information. She developed asthma at a young age. Until puberty she presented numerous febrile episodes interpreted as part of trivial pharyngeal viral infections which prompted no special medical attention. Since age 17 she has been experiencing recurrent self-limited minor oral aphthous ulcers. She continued to exhibit frequent febrile episodes, some in the context of various site infections (occurring in the absence of any identifiable cause for immunodepression), some unexplained (Mycobacterium tuberculosis infection was excluded), but the paucity of any relevant findings precluded a conclusive chronic multisystem disease diagnosis and prompted no specific treatment except for the adequate management of the infections and asthma. Subsequently, the clinical expression of her condition slowly expanded, having a waxing and waning course, and accumulating transient clinical features highly characteristic for two primary systemic predominantly small vessel vasculitides as well as several elements suggestive for systemic lupus erythematosus coexisting with antiphospholipid and secondary Sjögren's syndromes. The diagnosis of a chronic dysimmune spectrum disorder was strongly suspected at age 20 when during an episode of fever and subacute maxillary sinusitis the patient developed superior sagittal sinus thrombosis accompanied by laboratory findings consistent with antiphospholipid syndrome. At age 21 she developed acute appendicitis, successfully treated by surgical intervention (unfortunately, no pathological studies are available, thus its substrate is debatable). In the following months, prior to the initiation of chronic immunosuppressive therapy, dormant cytomegalovirus reactivation occurred, causing hepatic, intestinal, and possibly central nervous system involvement (cervical myelitis, discussed further on). Subsequently she developed persistent hemolytic anemia with low positive titers of warm antibodies and cold agglutinins coexisting with a persistent iron misutilization pattern characteristic for chronic inflammatory diseases. Occasionally a sideropenic component having various etiologies was superimposed. The emergence of the events listed above led to a constantly increasing number of hospital admissions, the patient being investigated and treated in infectious diseases, neurology and rheumatology departments. At age 22 she was referred to the Internal Medicine Clinic of our hospital where she has been successfully managed up to this day by a multidisciplinary team with expertise in collagen-vascular disorders. Since then she experienced recurrent brain and spinal cord involvement (discussed in detail further on). Her asthma became severe and unresponsive to the usual therapy which included high dose inhaled corticosteroids and long acting beta-2 agonists, tiotropium bromide, theophylline, and montelukast. She developed interstitial lung disease with lymphocytic alveolitis (characteristic computed tomography findings, decreased diffusing capacity of the lung for carbon monoxide and abundant lymphocytes in the bronchoalveolar lavage), fluctuating hepatopathy (hepatic cytolysis and cholestasis, no liver failure), nephropathy (laboratory findings consistent with glomerular dysfunction and proximal renal tubules impairment resulting in marked hypokalemia and renal acidosis, but no chronic uremia) and episodic intestinal inflammation in the absence of local infection. Sacroiliitis also occurred. During most of the exacerbations several of the above mentioned manifestations coexisted. Mild oral, ocular and nasal sicca symp-

toms with bilaterally positive Schirmer test and keratoconjunctivitis completed the picture. Intercurrent infections continued to be frequent. Outbreaks of herpes labialis accompanied the disease exacerbations and the infections in about a quarter of the cases. In the circumstance of severe immunosuppression (high disease activity plus iatrogenic), the patient developed Staphylococcus aureus sepsis thrice. Among the complications of the frequent prolonged courses of antibiotics she had several episodes of Clostridium difficile colitis. Superficial Candida albicans infections were also a common finding. All of the infections were treated promptly and successfully. Ever since she had the first thrombotic event at age 20, positive lupus anticoagulant test accompanied by resistance to activated protein C and by secondary decreases in protein C and S levels were constant findings (no factor V Leiden or other genetic thrombophilia were identified). After a second thrombotic event, occurring at age 22, she additionally developed serological changes consisting of persistent medium positive titers of immunoglobulin G anticardiolipin antibodies (42-48 immunoglobulin G phospholipid binding units – GPL-, measured by a standardized enzyme-linked immunosorbent assay). No immunoglobulin M anticardiolipin antibodies or anti-beta2 glycoprotein I antibodies were identified. Besides the already discussed laboratory work-up results, repeated extensive blood tests noted only very mild and rare changes comprising of elevated levels of the routinely measured acute phase reactants (in the absence of coexistent infections), positive titers of antinuclear antibodies (only twice, before the introduction of chronic immunosuppressive treatment, in the absence of any well established lupus-inducing drugs), positive titers of anti Ro/SS-A and anti La/SS-B antibodies (only once, during a severe disease flare-up), and decreased levels of the C3 complement fraction. Except for the central nervous system (discussed further on), exhaustive imagistic and ancillary investigations showed either no abnormal changes or nonspecific inflammatory findings (the latter on pulmonary computed tomography, colonoscopy and capsule endoscopy). Optical microscopy examination of the paranasal sinus mucosa and of the colonic mucosa disclosed no eosinophilic infiltrates, no granulomas and no small vessel vasculitis. Minor salivary gland biopsy was not performed (a negative result would not have excluded Sjögren's syndrome). Considering that invasive procedures involve additional risks in this immunosuppressed and anticoagulated patient and that enough evidence for an aggressive dysimmune inflammatory prothrombotic disorder existed, these kind of investigations were limited to those sine qua non for guiding therapeutic decisions, i.e. those important not only for circumscribing the diagnosis of the underlying disease but also for excluding potentially life-threatening comorbid conditions (e.g. neoplasia and infections, the differential diagnosis between non-infectious and infectious causes of clinical exacerbation being of crucial importance).

Since age 21 the patient fulfills the 2006 revised classification criteria for antiphospholipid syndrome (clinical 1, laboratory 1 and 2, without any additional classical risk factors for thrombosis) and since age 22 she also fulfills the 1997 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (from 7 to 11), as well as the 2002 internationally revised classification criteria for secondary Sjögren's syndrome (I, II, III, VI), therefore the diagnosis of an overlap syndrome between the above diseases being permitted (2,3,10,11). However this does not mean that such labeling is beyond doubt. The patient also presented with several clinical elements highly characteristic (but not pathognomonic) for two primary systemic vasculitides, i.e. severe asthma (unresponsive to conventional treatment but responsive to cyclophosphamide) for Churg-Strauss syndrome (7) and recurrent oral aphthous ulcers for Behçet's disease (12), so a more complex overlap syndrome would be actually implied. We note that the diagnosis of Churg-Strauss is not excluded by the absence of eosinophilia (in peripheral blood and/or tissue), by the absence of positive serum titers of perinuclear anti-neutrophil cytoplasmic antibodies (antimieloperoxidase subtype), and by the absence of any characteristic pathological findings at the above mentioned biopsy sites. We find appropriate to point out that the patient's childhood history (see above) may suggest the presence of PFAPA syndrome (i.e. periodic fever, aphthous stomatitis, pharingitis and cervical adenopathy), a non-hereditary self-limited autoinflammatory disorder associated with disturbances in the innate immunity (13-15). We also point out that the patient had a well documented symptomatic cytomegalovirus reactivation occurring prior to the initiation of immunosupresive treatment in the absence of any identifiable humoral signs and/or causes of immunodespression. It has been reported that cytomegalovirus replication may be triggered not only during decreased immune surveillance but also during immune overactivity, and that at the same time its presence may induce, initi-

ate and/or maintain autoimmunity and inflammation (16). We may speculate that cytomegalovirus infection, though actively treated (see below), may have played a role in the etiopathogenesis of our patient's dysimmune disorder. Over the years, the pathogenic treatment included: anticoagulant drugs (most of the time subcutaneous low molecular weight heparin, the administration of oral acenocoumarol not being feasible because of extreme difficulties in maintaining a stable therapeutic international normalized ratio – INR-, explainable either in the context of the antiphospholipid syndrome, or of the concomitant interacting medication, e.g. antiepileptics), anti-inflammatory drugs (methylprednisolone in low to moderate daily doses and in low to high-dose pulses during exacerbations), immunomodulatory drugs (hydroxychloroquine 400 milligrams per day; high-dose intravenous immunoglobulin during exacerbations inadequately controlled by high-dose pulse corticotherapy or associated with severe infections, case in which they proved to be a salutary solution; plasma exchange in one extremely severe circumstance accompanied by renal failure), and immunosuppressive drugs (high-dose intravenous methylprednisolone pulses during exacerbations; monthly pulses of 600 milligrams per square meter intravenous cyclophosphamide as disease-modifying treatment, switched after 6 pulses and 3 months of stable remission to methotrexate up to 20 milligrams per week, switched back to cyclophosphamide after 4 months because of severe disease exacerbation). The treatment was constantly adapted to the evolution of the disease. Symptom-relief and life-supporting interventions were used as required. Correct nutritional support and kinesiotherapy were provided. Adequate monitoring of the potential complications of the treatment and prophylactic approaches were instituted as advised in each particular case. No worth mentioning side effects occurred except for mild iatrogenic hypercortisolism (adipose tissue redistribution, striae distensae and mild cataract) and possibly gastritis and infection predisposition.

Cerebral venous system thrombosis/ thrombophlebitis

As already mentioned, the first cerebral venous system thrombosis occurred at age 20 during the evolution of a subacute bilateral maxillary sinusitis accompanied by asthma exacerbation, low grade fever, mild leukocytosis with lymphopenia, and moderate biological inflammatory syndrome. Two days after antibiotic therapy initiation the patient developed severe diffuse vascular-type headache, obtundation, paraparesis and subintrant alternating focal motor seizures, one with secondary generalization evolving towards generalized status epilepticus (managed accordingly in the acute setting). The brain magnetic resonance imaging (MRI) obtained during the same day was unremarkable except for loss of flow void in the superior sagittal sinus on T1-weighted images, while the contrast magnetic resonance venography (MRV) demonstrated absence of flow in the superior sagittal sinus, findings compatible with acute sagittal sinus thrombosis (images not available). Anticoagulation with intravenous unfractionated heparin was started and the intracranial hypertension was adequately treated. An extended release sodium valproate and valproic acid compound was chosen for the secondary prophylaxis of the epileptic seizures, the dose being gradually increased (as required) to the equivalent of 2000 milligrams of sodium valproate per day. Complete clinical resolution occurred in less than a month, except weekly episodes of vascular type headache (moderate in intensity and responsive to acetaminophen) which still persist. Though a possible local prothrombotic risk factor and even a potential source for pyogenic dissemination existed, the investigations included a thrombophilia panel which disclosed lupus anticoagulant, constantly positive ever since. She was continued on oral anticoagulant (acenocoumarol, target INR range 2 to 3, subsequently switched to subcutaneous enoxaparin 1 mg per kilogram every 12 hours for reasons already explained).

At age 22, during a lower urinary tract infection with Escherichia coli for which she was receiving specific antibiotic treatment, 2 days after the unwise discontinuation of the anticoagulant, the patient developed severe vascular-type headache. She presented to her local town hospital where one generalized self-limited seizure occurred (in spite of still receiving valproate as recommended). The following day, when first seen in our hospital, she was afebrile, in a stuporous state, with maximal bilateral mydriasis, bilaterally decreased pupillary light response, preserved blink reflex to visual threat, and intermittent simultaneous symmetrical inward and downward deviations of both eyes (unaccompanied by changes in her pupils size). No meningeal irritation or other relevant signs were found. She had normal blood glucose, acid-base equilibrium and electrolytes levels. Several minutes after hospital admission she developed refractory generalized convulsive status epilepticus which was managed according to the contemporary guidelines

and to the locally existing resources, the motor activity subsiding after anesthetic dose midazolam administration. Considering that the dose of midazolam could not be titrated against the electroencephalogram (EEG) burst-suppression pattern, the maximal dose of 0.4 milligrams per kilogram per hour was administered over the next 24 hours. The chronic antiepileptic medication (valproate 2000 mg per day) was supplemented by intravenous phenytoin (100 milligrams every 6 hours) the latter subsequently switched to 1000 mg per day oral levetiracetam. Osmotherapy with intravenous mannitol was initiated and continued over the next 5 days. The 0.5 Tesla open MRI machine that was available in our hospital permitted the manual ventilation of patients during the examination procedure, so a brain MRI with contrast MRV were promptly obtained. The findings were consistent with left thalamic and ipsilateral deep medial occipital non-hemorrhagic venous infarction/congestion secondary to bilateral thrombosis/thrombophlebitis of the basal veins of Rosenthal, extending to the great vein of Galen and straight dural sinus. The D-dimer titer was just above 12 times the upper reference range value, the activated partial thromboplastine time was prolonged, and the fibrinogen blood level was decreased, findings suggesting ongoing thrombosis. The anticoagulation with body weight-adjusted subcutaneous enoxaparin was promptly resumed. Nephropathy of the kind discussed above developed over the following days. In addition to the positive lupus anticoagulant repeatedly found on the previous testing, a positive titer of immunoglobulin G anticardiolipin antibodies (42 GPL) was identified. Enough arguments for life threatening antiphospholipid syndrome existed (17, 18), the aggressive thrombotic event probably being triggered (in the already discussed dysimmune setting) by anticoagulant withdrawal during ongoing infection. Anti-inflammatory and immunosuppressive therapy were considered (besides anticoagulation alone) and methylprednisolone pulse therapy was stared (total dose 3 grams, divided over 6 days, continued with 0.8 milligrams per kilogram per day). When the midazolam administration was temporarily discontinued (24 hours since its initiation) the patient regained consciousness but needed to remain on artificial ventilatory support (failure to maintain adequate breathing – Cheyne-Stokes with prolonged apnea). Her pupils were moderately mydriatic and responsive to light. The ocular movements were normal. She understood spoken language and could communicate by eye movements. She had tetraplegia accompanied by marked appendicular and axial hypotonia, brisk pendular stretch reflexes, and bilateral Hoffman's with indifferent plantar reflexes. Consequently, a difficult to control thalamic hyperpathia of the distal extremity of the right lower leg persisted for about two years. Her constantly improving condition allowed detubation after a week. The motor function slowly improved, but hypotonia, especially axial, persisted. Almost a month and a half since the onset of the events described above she developed renal dysfunction, hemolytic anemia, elevated liver enzymes (trice the normal) and persistent fine regular livedo reticularis. She was treated with enoxaparin, but mild laboratory findings suggesting active thrombosis persisted. A 3 grams methylprednisolone pulse was administered. Few days later severe headache appeared followed by a sequence of events almost identical to that described above (i.e. refractory generalized status epilepticus preceded by signs suggestive for diencephalic and/or mesencephalic dysfunction and intracranial hypertension with bilateral oculomotor and/or abducens compression, requiring intubation, anesthetic doses of midazolam and mechanical ventilation, followed by similar clinical findings and evolution). In addition to the prior medication intravenous cyclophosphamide pulse therapy was administered (600 milligrams per square meter divided over 4 days). Serological findings comprising of mildly increased levels of anti Ro/SS-A and anti La/SS-B antibodies were completed the laboratory picture. As in the case of the previous episode, the placement of a central venous catheter was required. Two weeks later Staphylococcus aureus sepsis developed, shortly followed by acute renal failure. After an initial improvement, the patient's global condition once again deteriorated. Adequate antibiotic therapy (meropenem, linezolid) and life supportive measures were initiated. Plasma exchange was performed (3 procedures over consecutive days, 1 plasma volume exchange per procedure). Low dose oral methylprednisolone was continued in addition to the anticoagulant treatment. After the complete resolution of the intracranial hypertension, active thrombosis and renal insufficiency, three intravenous immunoglobulin courses were administered one month apart (2 grams per kilogram per course, divided over 5 days). Eight weeks after the resolution of the septic event the intravenous cyclophosphamide and methylprednisolone pulses were resumed on a monthly schedule. No other disease exacerbation occurred during this period. The patient regained her baseline neurological status six months later.

At age 24, the patient developed gastritis with upper gastrointestinal hemorrhage resulting in moderate sideropenic anemia. Along with the other necessary measures the enoxaparin administration was reduced to the prophylactic dose. Two days later she awoke with severe vascular-type headache. She was obtunded. Her blood workup showed changes consistent with active thrombosis. The fundoscopic examination was normal. Later during the same day, while in a sitting position, she developed bilateral mydriasis accompanied by intermittent simultaneous inward and downward eye deviation similar to those described above. In less than two minutes she became unresponsive to stimuli (Glasgow Coma Scale 3). The EEG performed immediately prior and after the onset of the coma showed diffuse changes consisting of sharp alpha waves and moderate amplitude theta and delta waves with no epileptiform discharges (Figure 1). Her blood pressure, blood glucose and sodium levels were within normal range. Osmotherapy with mannitol was promptly administered (along with appropriate body positioning). The anticoagulation was resumed. Over the following hours her coma reversed to stupor which persisted for several days. During this time she presented a self limited tonic seizure. She had tetraparesis, 3/5 on the British Medical Research Council (BMRC) scale, and marked axial hypotonia. Emotional lability was observed when she fully regained consciousness. Methylprednisolone pulse therapy (3 grams) was administered in addition to the monthly cyclophosphamide pulse. Her neurological status returned to baseline during the following four weeks.

The patient has only scarce recollection from the first weeks following each of these latter events. A clinical picture compatible with pseudotumor cerebri (comprising of severe diffuse pulsatile headache made worse by clinostasis, emesis and visual blurring in the absence of other neurologic signs) but unaccompanied by papilledema (searched for at symptoms onset) emerged several times during non-neurologic exacerbations, while she was correctly anticoagulated and her D-dimer titer was within reference range. The brain computed tomography obtained during the first of these circumstances (images not available) revealed no significant changes. The symptoms were relief by intravenous mannitol and promptly remitted after low dose methylprednisolone pulses, paralleling the general favorable evolution.

Acute transverse myelitis

The first episode of acute transverse myelitis occurred at age 21 in the context of dormant cytomegalovirus reactivation (positive peripheral blood polymerase chain reaction, elevating specific immunoglobulin G titers, persistent moderate fever, hepatic and intestinal involvement). Cytomegalovirus is mainly opportunistic, however the patient's peripheral blood lymphocyte subtypes and the se-

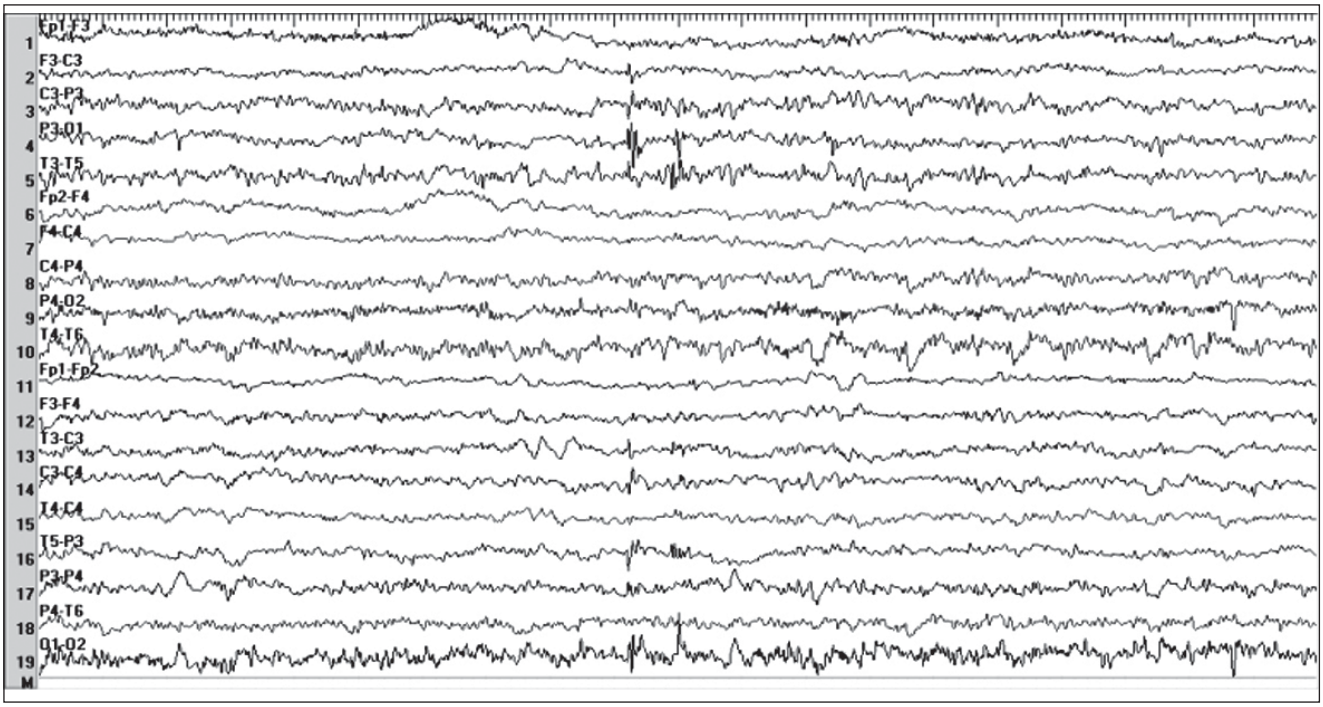

FIGURE 1. *Coma onset EEG. Portion of the EEG recording showing diffuse sharp alpha waves and moderate amplitude theta and delta waves predominantly in the right derivations.*

rum immunoglobulin fractions where within reference ranges. Extensive tests revealed no other viral infections and no potential cause for immunodepression. Over the course of 2 days severe tetraparesis, all modalities hypoesthesia below C6 and urinary retention developed. The routine cerebrospinal fluid analysis (collected during the first day since myelopathy onset) revealed no notable changes. Cerebrospinal fluid cytomegalovirus antigens, antibodies, and DNA polymerase chain reaction could not be performed. The MRI obtained on the second day since onset confirmed the presence of a gadolinium enhancing spinal cord lesion at the C6 level (images and detailed description not available), supporting the diagnosis of acute transverse myelitis (19). Considering the systemic context ganciclovir was given for an extended period of about 6 months. A course of intravenous immunoglobulin was concomitantly started (total dose 2 grams per kilogram, divided over 5 days). No improvement in the neurological status occurred. The hypothesis of a direct viral etiology of the myelitis was considered, but an autoimmune cause (multisystem or central nervous system restricted) could not be excluded. Imagistic exploration of the brain and other segments of the spinal cord could not be performed. No relevant serological changes were found except for a mildly increased antinuclear antibodies titer. Lupus anticoagulant was positive at moderate values (the patient received oral anticoagulant). Methylprednisolone pulse therapy was administered (total dose 5 grams, slowly tapered with low oral doses). Hydroxychlorquine was added as chronic immunomodulatory treatment. During the following weeks her neurological status improved, leaving behind only a T4-T7 residual hypoesthesia, persisting ever since.

At age 23, shortly after regaining normal clinical neurological status and after being switched from cyclophosphamide to methotrexate, the patient developed over the course of a few days flaccid paraparesis (BMRC 2/5) with brisk stretch reflexes, followed by all modalities hypoesthesia below T10 and urinary retention. The clinical picture was highly suggestive for complete acute transverse thoracic myelitis. No lumbar puncture and no imagistic investigations were performed. A 3 grams pulse of methylprednisolone was administered. Her condition rapidly improved, the patient returning to the previous neurological status over the next 3 weeks. This neurological event coincided with multisystem disease exacerbation. The methotrexate was stopped and the cyclophosphamide pulses were resumed.

At age 24, one month after maximally recovering from the last exacerbation, the patient awoke with intense non-pulsatile headache (restricted to the C2 dermatomes), accompanied by emesis, urinary retention and mild flaccid paraparesis with brisk stretch reflexes, bilateral Hoffman's and indifferent plantar reflex. She had recently missed one enoxaparin dose but her D-dimer titer was within normal range. The 0.5 Tesla brain MRI revealed no parenchymal changes and the MRV found a permeable cerebral and cerebellar venous system. During the next day the paraparesis exacerbated (BMRC 2/5) and bilateral brachial motor deficit completed the picture (right 3/5, left 4/5). We considered the clinical findings to be suggestive for cervical partial acute transverse myelitis. No spinal cord MRI was obtained. In addition to the monthly pulse of cyclophosphamide a total dose of 3 grams of intravenous methylprednisolone was administered. Marked improvement of all signs and symptoms occurred over the next two weeks.

Encephalopathy manifested as psychosis

At age 23, 24 and 25, while also experiencing non-neurologic disease exacerbations, the patient developed delusional thinking with paranoid ideation, marked reactive anxiety and agitation. She denied having hallucinations. Each of these times she stopped taking her valproate (but not her levetiracetam), and several rapidly self-limited unwitnessed episodes of consciousness loss, most likely generalized seizures, occurred. During the first two psychotic events she had episodes suggestive for temporal partial complex seizures. The neurological exam revealed no additional changes except for the preexisting residual impairments. The cognitive function was within normal limits according to the results of the Montreal Cognitive Assessment (30/30) and Mini Mental State Examination (30/30). Repeated EEGs showed no particular findings. She had no fever and no relevant hydroelectrolyte or metabolic disturbances (including normal blood ammonia levels, periodically tested considering the chronic valproate administration). Thyroid function was within normal limits, and serum anti thyroid peroxidase antibodies had negative titers. Except for the low dose daily methylprednisolone she was receiving no medication well established in inducing psychosis. The brain computed tomography obtained during the first event of this kind showed no relevant changes. The second event occurred three weeks after the onset of the latter cervical myelitis. A lumbar puncture was performed, the open-

ing pressure was normal and the routine cerebrospinal fluid analysis revealed no particular findings. A total dose of 1 gram of methylprednisolone divided over 4 days was administered each time (followed by her monthly cyclophosphamide pulses). Each time the patient returned to her previous status before the completion of the pulsed corticotherapy.

Pancerebellar syndrome accompanied by cerebellar atrophy

At age 24, during an episode of acute non-lithiasic cholecystitis for which she was receiving ceftriaxone, the patient presented with axial and gait ataxia and hypotonia progressing over the course of 3 days to inability to walk, stand, sit or hold her neck erect (in the absence of explicit muscle weakness). Symmetrical appendicular hypotonia with pendular osteotendinous reflexes, mild dysmetria, rebound phenomenon and bilateral horizontal nystagmus evoked by fixation and influenced by head tilt completed the picture. The proprioceptive and vibratory senses were intact. A contrast enhanced 0.5 Tesla brain MRI was obtained showing no relevant changes except for an apparent mild decrease in the cerebellar size, not present on the previous exams (Figure 2). Volumetric analysis was never performed, and when comparing with the subsequent MRI examination is difficult to appreciate if the atrophy has additionally progressed. The patient was anticoagulated and the D-dimer titer was negative. She had a moderate biological inflammatory syndrome. Her serum C3 fraction was decreased and the lupus anticoagulant and immunoglobulin G anticardiolipin antibodies were positive. The usual immunology panel revealed no other changes. Considering that since the onset of her above mentioned digestive condition she could no longer tolerate oral valproate (it constantly induced emesis shortly after ingestion) and that parenteral preparations were not available she had been switched on intravenous phenytoin. The peak phenytoin blood levels were within therapeutic range, nevertheless a potential toxic effect as cause of the cerebellar syndrome could not be excluded, so as soon as possible the patient was switched back on valproate. She still received oral levetiracetam, which she could tolerate. She had a mild decrease in electrolyte levels, adequately corrected. In the two weeks prior to the onset of the neurological symptoms she had inadequate nutritional intake (in the context of frequent emesis), therefore intravenous thiamine (600 mg per day) was promptly administered after the development of axial ataxia. Her condition continued to deteriorate (in spite of the thiamine administration, correction of hypomagnesaemia, and parenteral nutritional support) therefore not supporting a Wernicke's Encephalopathy diagnosis (20). The chronic low dose of methylprednisolone was augmented to a total dose of 1.5 grams administered over the next 3 days. Only little improvement occurred. Her monthly cyclophosphamide pulse, temporized because of her supposed infection, was administered shortly after. Three weeks after the methylprednisolone pulse therapy her cerebellar syndrome exacerbated. Another 1.5 grams of methylprednisolone were administered followed by the monthly dose of cyclophosphamide. Only a modest neurologic improvement was observed. Ten days later a pulse of intravenous immunoglobulin was administered (total dose 2 grams per kilogram). Over the next two weeks the patient became able to sit and stand with unilaterally support. During the next three months her neurological status reached previous levels. At 25, she experienced two similar but milder episodes of cerebellar involvement, the first accompanied by recurrent vascular-type headache and both accompanied by rapidly fluctuating mood ranging from mild euphoria to depression. As in the previous case the axial involvement was the most pronounced, however the patient was able to sit, stand with widened base, and walk with in-

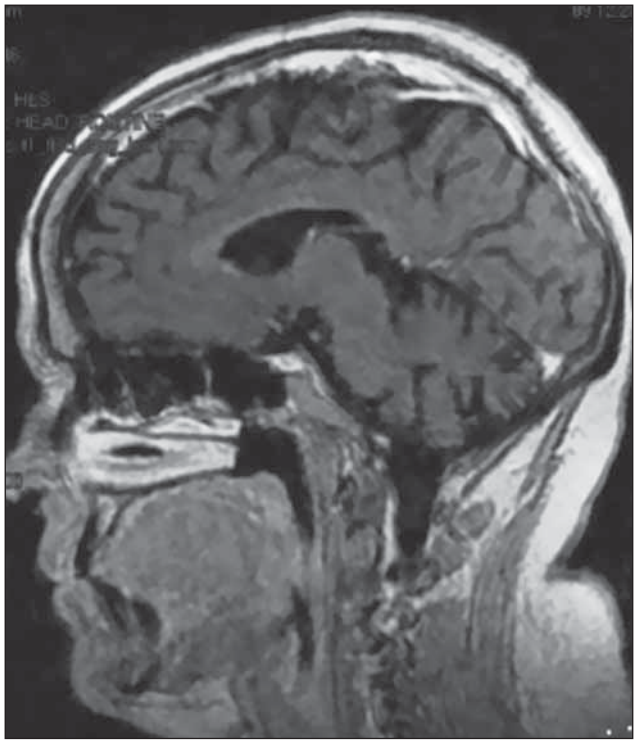

FIGURE 2. *Brain MRI revealing cerebellar atrophy. Sagittal T1 weighted gadolinium enhanced section showing a mildly decreased size cerebellum*

termittent unilateral support. Neither of these times she was receiving phenytoin. Her antiepileptic blood levels were within therapeutic ranges and the usual immunological workup brought no additional information. The administration of a total dose of 1 gram of methylprednisolone was followed by rapid improvement in each case the patient returning to the previous neurological status in less than a month.

Present status

At the time of this writing the patient is progressively recovering from the last and the most severe exacerbation of the disease. While in apparent remission, three months after switching from intravenous monthly pulses of cyclophosphamide to daily oral doses cumulating 800 milligrams per square meter per month, shortly after the onset of multiple site infections (urinary tract infection with Escherichia coli, intestinal infection with Clostridium difficile and non-lithiasic cholecystitis, all of them treated accordingly and cured), the patient developed difficult to catheterize urinary retention. Two days later flaccid paraparesis emerged, initially mild, but progressing over about 24 hours to BMRC 2/5. These findings were subsequently accompanied by all modalities sensitivity impairment below T7, thus outlining a clinical picture compatible with partial acute transverse myelitis. The patient was treated with enoxaparin (1 milligram per kilogram each 12 hours) and was adequately hydrated. No imagistic spinal cord studies could be performed. Intravenous high dose methylprednisolone was started (500 milligrams per day during the first 3 days, 250 milligrams per day during the next 4). On the seventh day, after an initial improvement in the motor function, the patient developed excruciating diffuse pulsating headache (in the absence of meningeal irritation signs) accompanied by altered level of consciousness (progressing over the course of 12 hours from excessive somnolence to obtundation and stupor). Concomitantly her sicca symptoms markedly exacerbated. Direct ophthalmoscopy disclosed papilledema with venous engorgement (no arguments for retinal venous thrombosis were found on repeated examination and the fundoscopic changes remitted while the clinical picture of intracranial hypertension improved). She associated severely impaired vision in both eyes (the pupillary light reflex was initially preserved but rapidly became markedly diminished). While stuporous the patient developed bilateral maximal convergent strabismus, initially unrhythmically intermittent, subsequently persistent. In the previous day she experienced episodic binocular intermittent diplopia which she didn't report at that time. These involuntary eye movements (horizontal, slow and sometimes slightly asynchronous, accompanied neither by mydriasis, nor by rapid progression to coma, i.e. different from those described above that occurred in the setting of deep cerebral venous system thrombosis) were initially interpreted as the onset of bilateral abducens palsy caused by compression in the context of intracranial hypertension. Voluntary vertical eye movements were not possible but they were elicited by vestibular stimulation (flexion-extension of the neck). Osmotherapy with intravenous mannitol was started and the administration of enoxaparin and methylprednisolone was continued, the latter up to a total dose of 4.5 grams followed by 0.8 milligrams per kilogram per day. No seizure occurred, however the patient was still under maximal antiepileptic treatment. The level of consciousness and the visual function returned to normal one day later but the severe headache persisted. Marked axial and appendicular hypotonia with pendular reflexes developed and signs of neocerebellar dysfunction became apparent in the upper limbs (unaffected by muscle weakness). The 0.5 Tesla brain MRI (performed on the third day since the onset of the symptoms suggesting cerebral venous system thrombosis) revealed an acute to subacute stage non-obstructive thrombus in the left transverse dural sinus (Figure 3A) extending over about 2 centimeters. The contrast MRV revealed significant loss of flow in the ipsilateral transverse sinus and downstream the ipsilateral sigmoid sinus (Figure 3B). No brain parenchymal lesions were found (not even cytotoxic or vasogenic edema as reflected by the diffusion weighted images corroborated with the apparent diffusion coefficient maps). The patient was switched on continuous intravenous unfractionated heparin with target partial activated thromboplastin time ratio between 2 to 2.5 (therapy maintained for two weeks, switched back to enoxaparin because of the development of mild thrombocytopenia, subsequently remitted). The evolution was favorable except for the extraocular motility impairment and sicca syndrome which continued to exacerbate. The bilateral convergent strabismus persisted and slightly asymmetric blepharoptosis developed over the next day. The coexisting clinical findings were highly suggestive for local neuromuscular junction dysfunction (i.e. active extraocular muscle contraction resulted in the exacerbation of ptosis and/or in concomitant lagophthalmos, initially with noticeable upward deviation of both

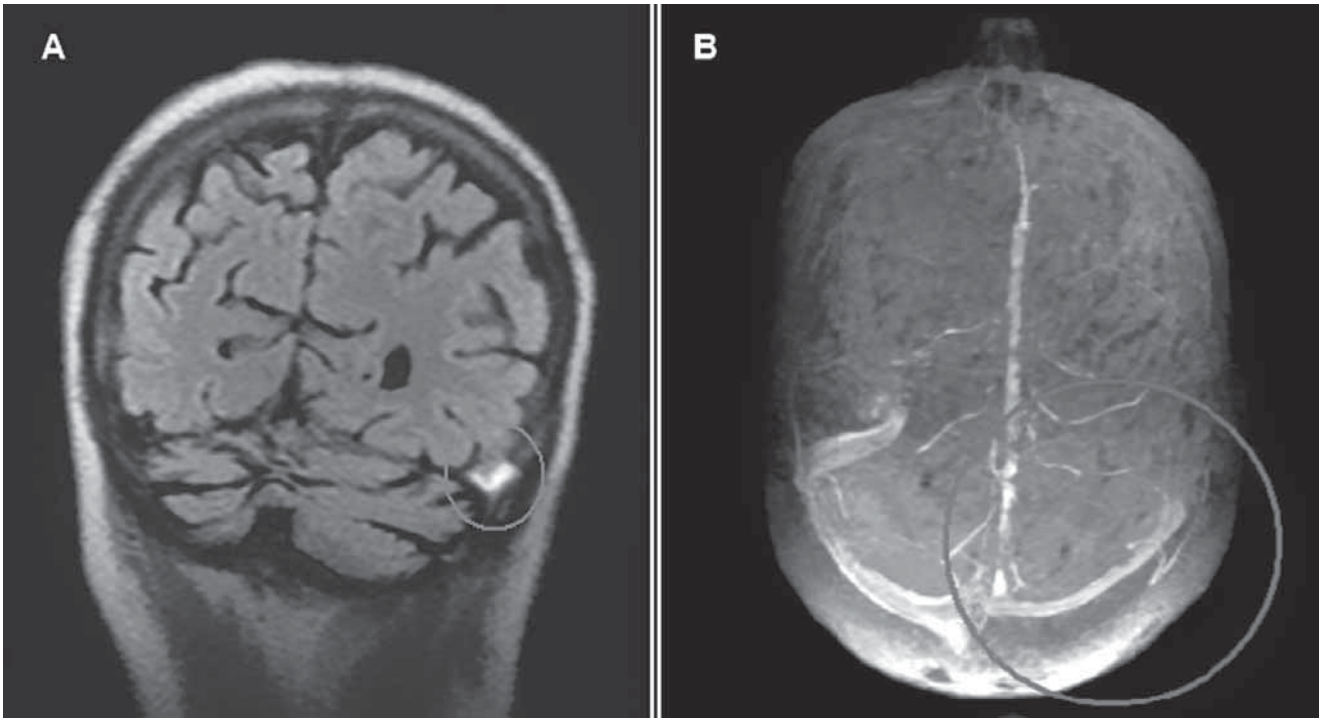

FIGURE 3 A-B. *Brain MRI with MRV revealing left transverse dural sinus thrombosis. Coronal fluid attenuated inversion recovery (FLAIR) brain MRI demonstrating hiperintensity in the left transverse dural sinus consistent with subacute thrombus (A) and cerebral contrast MRV demonstrating loss of flow in the left transverse dural sinus and downstream the ipsilateral sigmoid sinus (B)*

strabic eyes – considered to be Bell's phenomenon – which also fatigued; these were alleviated by rest). All of the ocular signs (including the above mentioned bilateral convergent strabismus) temporarily resolved following a 1 milligram parenteral neostigmine test dose therefore providing solid arguments for the presence of a myasthenic syndrome. Considering the sicca syndrome the neostigmine administration was not backed-up by the usual antimuscarinic drug and during the test the severe hyposalivation also promptly resolved (and interestingly to note the patient displayed no signs of parasympathetic overactivity). No electromyographic studies could be performed yet. The blood levels of nicotinic acetylcholine receptor antibodies (anti-AChR), anti-striational antibodies (or anti-titin and anti-ryanodine), anti-muscle specific kinase antibodies (anti-MuSK) and anti-voltage gated calcium channels (anti-VGCC) could not be assessed yet. The patient was switched on oral pyridostigmine (up to 60 milligrams 6 times per day), but in spite of the important subjective and objective improvement the sustained activity of the extraocular muscles still lead to local fatigability, resulting in fluctuating degrees of unilateral or bilateral, horizontal and/or vertical ophtalmoparesis. The monthly cyclophosphamide dose was supplemented by a total dose of 600 milligrams given intravenously over three days (equivalent of a total dose of 1200 mg per square meter over the last month), subsequently the monthly pulsed administration being resumed. While the upper limbs cerebellar sings resolved, the paraparesis improved and the headache significantly diminished, the fluctuating ocular motility findings persisted and fluctuating dysphonia, hypophonia and fatigability of the neck extensors also appeared. These bulbar and cervical axial signs were also responsive to neostigmine administration. A total dose of 2 grams per kilogram of intravenous immunoglobulin (medication unavailable up to this point) was administered resulting in obvious improvement of the myasthenic phenomena and also of the sicca syndrome. Extensive ancillary investigations were performed (including screening for occult infections and neoplasia) but at no time during this severe disease flare-up they disclosed any additional relevant findings. Two days after the discontinuation of the intravenous immunoglobulin the paraparesis once again exacerbated. Upper limbs paresis (right BMRC 3/5, left 4/5) accompanied by local pyramidal signs (absent until then), by an additional superficial cutaneous sensory deficit in the right T1-T6 dermatomes and by urinary retention in the presence of a correctly placed permeable transurethral catheter appeared during the same day, thus sug-

gesting the development of a new spinal cord lesion. Exacerbation of the myasthenic syndrome (fluctuating blepharoptosis, lagophthalmos, variable ophtalmoparesis, dysphonia, hypophonia, and neck extensor fatigability) and of the sicca syndrome (this time accompanied by bilateral dacryoadenitis) rapidly followed. High dose methylprednisolone therapy was once again started (250 milligrams per day) augmenting the recent administered dose by another 2 grams (subsequently tapered to 0.8 milligrams per kilogram per day). Almost a month since the onset of this neurological exacerbation, while receiving her intravenous cyclophosphamide pulse, high fever accompanied by laboratory signs suggestive for bacterial infection (most likely having as entry point the central venous catheter) occurred. The cyclophosphamide administration was ceased and the infectious event was controlled by prompt wide spectrum antibiotic therapy, nevertheless myasthenic exacerbation accompanied by sicca syndrome aggravation rapidly followed. A total dose of 1.33 grams per kilogram of intravenous immunoglobulin was administered. The neurologic and general status of the patient stabilized and subsequently began to improve. At almost two months since their onset, the ocular and bulbar myasthenic features persist.

DISCUSSION

Cerebral venous system thrombosis seems to account for less than 1% of all strokes, having a peak incidence in young adults. It usually involves the sagittal sinuses and/or cortical veins, deep cerebral venous system thrombosis resulting in infarct being a very rare occurrence (21). Regardless of the involved site it presents with headache in up to 90% of the cases (sometimes thunderclap), with focal and/or generalized seizures in up to 40% of the cases and with focal neurological deficits (including seizures) in 40 to 60% of the cases (22). Cerebral venous system thrombosis has been reported to occur in the setting of several inflammatory and/or thrombophilic disorders including systemic lupus erythematosus (23), antiphospholipid syndrome (10), and Sjögren's syndrome (24). A case of superior sagittal sinus thrombosis in the setting of Churg-Strauss syndrome has also been described in the literature (25). Dural sinus thrombosis is considered to be a major manifestation of Behçet's disease having a prevalence of 10 to 12% among neuro-Behçet patients (26). The characteristics of Behçet's disease related cerebral venous thrombosis were described on a series of 64 patients (representing 7.8% from a cohort of 820 Behçet disease patients), the authors concluding that a few particular features may be encountered in this setting, including a more insidious onset, with persistent headache progressing over a few days (versus acute) and a lower incidence of other signs and symptoms, focal deficits and seizures occurring in only 8% respectively 5% of the patients (26). Isolated intracranial hypertension has also been described as an occasional modality of presentation (27). The venous thrombosis was the initial manifestation of Behçet's disease in 20% of the patients, and occurred more frequently in males (unlike the usual situation). Associated prothrombotic factors were found in 31% of the patient, little less than a third of these presenting antiphospholipid antibodies, nevertheless their potential etiopathogenic role has not been established (26). Among the patients with cerebral venous thrombosis a 5 times lower rate of Behçet disease related brain parenchymal involvement was found along with a higher rate of other sites thrombosis (6, 26, 27). Sequelae occurred in almost a third of the treated patients and relapse in 11%, both of these being higher rates than those found in cerebral venous thrombosis appearing in other settings. Both the presence of sequelae and of relapse was associated with a poorer prognosis (28). The etiopathogenesis of the vascular involvement caused by Behçet's disease is considered to be mainly inflammatory and it comprises not only of arterial and venous stenosis/occlusion but also of aneurism formation, reason for which the recommended approach in Behçet's disease related cerebral venous system thrombosis (/thrombophlebitis) used to be anti-inflammatory and immunosuppressive therapy alone (26). According to the above mentioned report acute and chronic anticoagulation in Behçet's disease related cerebral venous system thrombosis was associated neither with a worse prognosis of the thrombotic event, nor with fatal hemorrhagic complications, and when compared with anticoagulation alone the administration of immunosuppressant drugs did not improve the neurological outcome or the thrombosis relapse rate (26,28,29). However, the concomitant use of anticoagulation and short-term corticosteroids with or without immunosuppressants is advocated by some (30). Regarding the treatment of cerebral venous thrombosis in the setting of systemic lupus erythematosus with or without antiphospholipid syndrome the use of both corticosteroids and anticoagulation is recommended (23). The European Federation of Neurological Societies (EFNS) guideline on the treatment of cerebral venous and

sinus thrombosis in adult patients recommends indefinite time length anticoagulation in those with a persisting precipitating factor but makes no special remarks regarding thrombosis/thrombophlebitis occurring in the setting of systemic vasculitis (22). Recurrent headache is a frequent sequelae of cerebral venous system thrombosis, nevertheless it also has high incidence in the general population of those with systemic lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome and Behçet's disease (2,10,22,27,31). In our patient the headaches were not severe however the administration of valproate may have contributed to their control. Pseudotumor cerebri has been reported in the setting of Behçet's disease in the absence of identifiable cerebral venous system thrombosis (6, 27), as may have occurred in our patient. Generalized convulsive seizures are a relatively common complication of superficial venous system thrombosis, but are rare when only the deep venous system is involved (22, 32), situation in which involuntary movements with a non-epileptic substrate are more likely to be observed, i.e. decerebrate posturing. In the case of our patient the possible existence of previous epileptic focus/foci and the possible persistence of an inborn decreased seizure threshold, may explain the predilection for status epilepticus especially in the setting of acute brain injury. Our patient presented refractory generalized convulsive status epilepticus twice, both times without a definite clinically observable focal onset and both times in the setting of acute bilateral diencephalic injury caused by deep venous system thrombosis. Diencephalic disturbance resulting in abnormal signaling through the thalamocortical circuits has been proposed as a possible cause for the triggering and/or maintaining of the primary generalized seizures (i.e. so called centrencephalic seizures), however convincing evidence for such a mechanism were gathered only for absence type seizures (33, 34). We may speculate that in our patient the relationship between these two events (i.e. deep cerebral venous system thrombosis and generalized status epilepticus) is more than mere coincidence. We point out that our patient never experienced seizures outside the disease exacerbation periods however she is under antiepileptic treatment so the significance of this fact cannot be assessed. Nevertheless, we draw attention to the concept of autoantibodies mediated epilepsies that has recently been proposed in the literature as a corollary to the observation that seizure occur more often in the presence of certain autoantibodies directed against neuronal cell surfaces antigens, including anti voltage-gated potassium channel (VGKC) complex, anti N-methyl D-aspartate (NMDA) receptor, anti gamma-aminobutyricacid (GABA) B receptor, and anti α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (35). These antibodies were not searched for in our patient.

Cytomegalovirus myelitis has been reported in immunocompromised patients and seldom in immune competent hosts (36). Testing for viral genome, antigens or antibodies in the cerebrospinal fluid was not performed in our patient and no indirect evidence suggesting viral presence within the central nervous system was found (normal immunoglobulin G index and negative oligoclonal bands). Therefore the viral or exclusively viral etiology of the first episode of acute transverse myelitis remains questionable, even more so if considering the above mentioned hypothesis of autoimmunity triggered and/or maintained by cytomegalovirus infection (16). Myelopathy consistent with partial or complete acute transverse myelitis has been reported to occur in the setting of systemic lupus erythematosus with or without antiphospholipid syndrome, and also in Sjögren's syndrome and Behçet disease (2,10,22,27,31). Except for the first myelopathic event the investigations required by the diagnosis criteria for acute transverse myelitis were not performed in our patient, nevertheless considering the clinical picture and the prompt response to high dose corticotherapy we consider that the designation of her distinct myelopathies as recurrent acute transverse myelitis is fairly supported. Considering the low quality of the brain MRIs performed the absence of non-vascular parenchymal brain lesions in our patient cannot be affirmed beyond reasonable doubt. Recurrent myelitis may be the presenting feature of relapsing remitting multiple sclerosis, nevertheless our patient does not fulfill the space and time dissemination requirements of the 2010 revision of the McDonald diagnostic criteria (37). A multiple sclerosis-like picture has been reported in the setting of systemic lupus erythematosus, antiphospholipid syndrome and Sjögren's syndrome (occurring together or independently). It remains debatable in which cases this represent the neurological expression of the multisystem disease and in which cases it represent an association between two distinct diseases (i.e. multiple sclerosis and a multisystem disease), with or without overlapping central nervous system involvement (38). Neuro-Behçet disease with a relapsing remitting and progressive pattern has been reported to masquerade as the corresponding type of multiple sclerosis (39). Considering that ade-

quate imagistic studies are not available the structural characteristics of our patient's myelopathy are not known, and the presence of extensive longitudinal myelitis cannot be excluded. Extensive longitudinal myelitis has been reported in association with systemic lupus erythematosus, antiphospholipid syndrome and Sjögren's syndrome (2,10,22,27, 31). According to the current guidelines if serum or cerebrospinal fluid anti-aquaporin-4 antibodies (immunoglobulin G) are found, an extensive longitudinal transverse myelitis may be classified as space limited neuromyelitis optica spectrum disorder (40). Unilateral or bilateral retrobulbar optic neuritis sometimes occurs in patients which also (simultaneously or not) have myelitis, resulting in situations fulfilling the current diagnosis criteria for neuromyelitis optica. Especially in the absence of anti-aquaporin-4 antibodies it remains an open discussion in which cases the association between the optic neuritis and the myelitis is the expression of the same pathogenic pathways and in which is not, and when the former situation holds true in which cases the involved pathogenesis is that of neuromyelitis optica and in which cases is that of another disease (40). Leaving aside the visual disturbances occurring in the setting of intracranial hypertension, symptomatic optic nerve involvement did not occur in our patient. The presence of anti-aquaporin-4 antibodies was not tested.

Psychosis has been reported in the setting of systemic lupus erythematosus, Sjögren's syndrome and Behçet disease (2,10,22,27,31). In some of the cases the psychiatric manifestations may be caused by the psychopathologic reaction to the disability and burden caused by the disease or may be coincidental. Causes of secondary psychosis include coexistent metabolic disturbances related to endocrinopathies, nutritional deficiencies and toxicities (iatrogenic or not). Brain damage may manifest as psychosis, and an organic substrate may exist even in the absence of identifiable structural changes, possibly mediated via autoantibodies and/or cytokines (41). We cannot affirm the absence of any relevant structural brain lesions in our patient at the time of the psychotic episodes. The presence of serum and/or cerebrospinal fluid anti ribosomal protein P antibodies, anti VGKC and anti NMDA, reported by some to be associated with autoimmune psychiatric syndromes, was not assessed (42). Antineuronal antibodies have been found in the sera of patients with psychiatric manifestation and Sjögren's syndrome (43), but they were not searched for in our patient. The rapid resolution of the psychiatric symptoms after the initiation of low dose methylprednisolone pulse therapy may be considered an argument for the direct relationship between the episodes of psychosis and the dysimmune status. Nevertheless, one may speculate that such a rapid remission of symptoms as the one that was observed in our patient may be related with the non-genomic effects of the glucocorticoids (44), therefore not necessarily reflecting their anti-inflammatory and immunosuppressive consequences.

In our patient is difficult to assess the substrate of the cerebellar syndrome, nevertheless we may affirm that extensive structural lesions were not present and that over the years the patient developed mild cerebellar atrophy, which may or may not be related with the (at least!) three episodes of reversible pancerebellar syndrome. Cerebellar dysfunction related to various types of structural lesions may of course occur in the setting of several dysimmune disorders. Cerebellar ataxia has been reported to occur in systemic lupus erythematosus and Sjögren's syndrome even in the absence of obvious structural lesion, anti-glutamate decarboxilase and anti neuronal antibodies being identified in one respective two patients with the latter disease (45). A case of subacute cerebellar ataxia associated with cerebrospinal fluid antineuronal antibodies occurring in a systemic lupus erythematosus patient in the absence of malignancy has been described (46). Recurrent acute cerebellar ataxia, having as possible underlying cause either vasculopathy or non-vascular neurotoxicity, has also been reported in the presence of anticardiolipin antibodies (47). Autoantibody associated cerebellar ataxia is more frequently triggered in a neoplastic context. The most commonly found antibodies in paraneoplastic cerebellar ataxia are anti Yo, but antibodies to other neuronal or glial antigens such as anti-Hu, anti CV2/CRMP5, anti Tr, anti Ri, anti Zic, anti proteinkinase C gamma, anti mGluR1, anti neuronal nuclear antibody-3, and anti voltage gated calcium channels may be found (45,48). Antibodies to gliadine, glutamate decarboxilase, tissue transglutaminase, glutamate receptor delta-2, and Homer have been encountered in patients with non-paraneoplastic autoimmune cerebellar ataxia (45,48). Recently a novel antibody against Purkinje cell somata has been characterized in one patient (48). In our patient no arguments existed for an associated neoplasia disease. The presence of any of the above mentioned antibodies has not been assessed. Findings characteristic for celiac disease were not present in our patient, nevertheless cerebellar ataxia associated with anti-gliadin antibodies may occur in

the absence of intestinal involvement (45). The presence of anti-gliadin antibodies was not assessed. Immune cerebellar ataxia has also been reported in the context of steroid-responsive encephalopathy associated with autoimmune thyroiditis (45), nevertheless no arguments for such a diagnosis existed in our patient. The treatment of non-neoplastic autoantibodies associated cerebellar ataxia is mostly immunomodulatory and/or immunosupressory and may vary according to the context. The complete resolution of symptoms as occurred in our case is not the usual course. We note that Purkinje cells have been reported to have the ability of internalizing immunoglobulin (48) along with reminding the apparently favorable outcome of the first pancerebellar event of our patient after intravenous immunoglobulin administration. Recurrent seizures have been suggested to be involved in the development of cerebellar atrophy (49) and may be considered as a potential causative factor in our patient. Moreover the potential contributory role of phenytoin, at least to the development of the cerebellar atrophy (if not also to the first episode of cerebellar dysfunction), should be taken into account in our patient (49). We remind that the patient also presented cerebellar syndrome in the context of deep cerebral venous system thrombosis. We may speculate that the subsequently found atrophy may be a consequence of this event, possibly secondary to a mechanism of crossed cerebellar diaschisis occurring in the acute setting, nevertheless in these situations significant contralateral supratentorial atrophy also occurs, finding not readily apparent in our patient on the MRI examination that initially disclosed the cerebellar atrophy (50).

The acquired autoimmune myasthenic syndromes are relatively uncommon conditions comprising of myasthenia gravis with its various subtypes and Eaton-Lambert myasthenic syndrome. Both of these have been reported to appear in association with other autoimmune diseases, nevertheless the latter is more frequently an autoimmune paraneoplastic disorder (8, 9). The electrophysiologic and serologic attributes of our patient's myasthenic syndrome have not been assessed, however a thorough screening revealed no signs of neoplasia (the presence of anti-SOX1 antibodies could not be tested). We remind that during the last disease exacerbation the patient exhibited both myasthenic syndrome and cerebellar dysfunction (in the absence of local MRI detectable lesions) along with the remark found in the literature that in the presence of anti-voltage gated calcium channels antibodies the cerebellar ataxia may coexist with Eaton-Lambert myasthenic syndrome (51). It is interesting to note that in our patient's case the development of the myasthenic syndrome coincided with the occurrence of the most severe sicca syndrome aggravation, and that the intensity of these two manifestations appeared to have a parallel evolution. It has recently been proposed that the action of anti-M3 muscarinic acetylcholine receptor antibodies found in the serum of patients with Sjögren's syndrome may explain the severe hyposalivation, dysfunction considered to be not attributable to the inflammatory glandular destruction (4, 52). Because of local particularities (including the pattern of receptor upregulation), these autoantibodies may have different functional impact on smooth muscle and exocrine cells, thus possibly explaining several of the autonomic dysfunctions encountered in patients with Sjögren's syndrome (53). It has been reported that the actions of anti-M3 muscarinic receptor antibodies are neutralized by the antiidiotypic antibodies present in pooled immunoglobulin, this raising the hypothesis that their occurrence may be favored by the absence of antiidiotypic antibodies in diseased individuals (54). Regarding our case (that displayed the immune deficiency features discussed above) we may speculate that the development of pathogenic antibodies may have been permitted by a deficiency in the production of antiidiotypic antibodies which in return may justify the apparent beneficial effect of the intravenous immunoglobulin administration. As known, the nicotinic and muscarinic acetylcholine receptors are structurally different, however, autoantibodies against M1 muscarinic acetylcholine receptor have been described in the serum of patients with acquired myasthenic disorders and may play a role in the pathogenesis of the neuromuscular junction dysfunction by modulating presinaptic phenomena (55).

CONCLUSION

Summing up the above, the patient presented with a particularly increased susceptibility to infections and with chronic fluctuating multisystem involvement having its onset around age 17. We consider that the former aspect may signify immune deficiency (congenital and/or acquired), while the latter may be explained by an autoimmune substrate, mainly with inflammatory consequences, but also with a significant prothrombotic component. Autoinflammatory mechanisms may have also contributed to the pathogenesis. Interesting to note is the infectious setting in which most of the exacer-

bations of the disease occurred. We may speculate that an overabundant infectious stimulus (in itself a probable indirect consequence of the disease) may have primed a genetically susceptible immune system into triggering simultaneously and/or successively several convergent and/or parallel pathogenic pathways resulting in a complex dysimmune disorder which would not merely be the association of a few independent diseases but a true overlap, having, as discussed above, elements suggestive for systemic lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome, Behçet disease and Churg-Strauss syndrome. The patterns of central nervous system involvement that occurred in our patient may be more or less commonly found in the setting of one or more of the above mentioned diseases except for the latter, in which they would be an exceptional occurrence (1,6,31,56). We may speculate that the pathogenesis of the nervous system involvement in our patient is mainly autoantibody and cytokine mediated, either predominantly inflammatory, as would be in the case of acute transverse myelitis, predominantly thrombotic, as may be in the case of the venous system thromboses (or even thrombophlebitis), or predominantly functional (autoantibody mediated) as may be the cases of the myasthenic syndrome, cerebellar dysfunction and psychosis.

In conclusion, we note that a peculiarity of this case is not necessarily the uncommon collection of different patterns of nervous system involvement in an unusual multisystem dysimmune disorder but the high degree of reversibility of all the neurologic impairments over time. To the best of our knowledge no similar case has been previously reported. We point out that some of the features observed in our patient may have been coincidental, while the aggressive treatment may have prevented the emergence of a more characteristic presentation for either of the discussed chronic disorders, not only shifting the picture towards milder manifestations but also changing it. It is our opinion that in the face of such complex situations one must not pursuit a definite diagnosis at all costs and should remain cautious in labeling the disease/diseases while not failing at promptly and correctly identifying the type and degree of organ involvement and at treating the patient accordingly, dynamically tailoring the therapeutic management to the clinical evolution.

Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

List of abbreviations used

PFAPA – periodic fever, aphthous stomatitis, pharingitis and cervical adenopathy
GPL – immunoglobulin G phospholipid binding units
INR – international normalized ratio
MRI – magnetic resonance imaging
MRV – magnetic resonance venography
BMRC – British Medical Research Council
EEG – electroencephalography
AChR – (nicotinic) acetylcholine receptor
MuSK – muscle specific kinase
VGCC – voltage gated calcium channels
EFNS – European Federation of Neurological Societies
VGKG – voltage-gated potassium channel
NMDA – N-methyl D-aspartate (NMDA)
GABA – gamma-aminobutyricacid
AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
FLAIR – fluid attenuated inversion recovery

Competing interest

The authors declare that they have no competing interest.

Authors' contribution

All authors have made substantial contribution to the acquisition, analysis and interpretation of the data and to establishing the presentation design. LD has been involved in drafting the manuscript. AN and BOP have been involved in drafting the manuscript and in revising it critically for important intellectual content concerning their expertise field. BOP has coordinated the work. All authors have read and approved the final manuscript.

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